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(54) Title: DRUG METABOLIZING ENZYMES

(57) Abstract: The invention provides human drug metabolizing enzymes (DME) and polynucleotides which identify and encode DME. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with aberrant expression of DME.

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Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
1	2434655CD1	527	S3 T120 T169 T200 S435 T520 S70 S343 S62 T141 T204 T243 T258 S296 S297 T419 Y130 Y143	N131 N313 N518	Signal peptide: M1-C23	HMMER
					Signal cleavage: M1-C23	SPScan
					Transmembrane domains: V91-N111, I492-F512	HMMER
					UDP-glucoronosyltransferase: G24-K525	HMMER-PFAM
					UDP-glycosyltransferases BL00375: A: S34-L56; B: C125-P165; C: P188-N211; D: I253-C280; E: F293-P342; F: N348-P392; G: H447-H486	BLIMPS-BLOCKS
					UDP-glucoronosyl and UDP-glucosyl transferases signature: N376-T417	ProfileScan
					UDP-glucoronosyltransferase (PD000190): G24-K338, V386-E527	BLAST-PRODOM
					UDP-glucoronosyl and glucosyl transferases: DM00367|P36510|176-459: M178-F460	BLAST-DOMO
					UDP-glucoronosyltransferase signature: W354-Q397	MOTIFS
2	2516747CD1	523	S107 S81 S95 T99 S126 S213 S219 T224 S374 S59 S133 S362 S409 T423 Y74 Y433	N52	Signal peptide: M1-A22	HMMER
					Signal cleavage: M1-L19	SPScan
					transmembrane domain: Y484-C503	HMMER
					UDP-glucoronosyl and UDP-glucosyl transferase: A23-K521	HMMER-PFAM
					UDP-glucoronosyl and UDP-glucosyl transferases signature: N373-T416	ProfileScan
					UDP-glycosyltransferases BL00375: A: S34-L56; B: C121-P161; C: P180-N203; D: L246-E273; F: N345-P389; G: L444-Q483	BLIMPS-BLOCKS
					UDP-glucoronosyltransferase: PD000190: K24-G291, L246-D430, L422-K522	BLAST-PRODOM
					UDP-glucoronosyl and UDP-glucosyl transferases: DM00367|P36513|188-462: L177-V456	BLAST-DOMO

using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Nucleic Acids Symp. Ser. 7:215-223; and Horn, T. et al. (1980) Nucleic Acids Symp. Ser. 7:225-232.) Alternatively, DME itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solution-phase or solid-phase techniques. (See, e.g., Creighton, T. (1984) Proteins, Structures and Molecular Properties, WH Freeman, New York NY, pp. 55-60; and Roberge, J.Y. et al. (1995) Science 269:202-204.) Automated synthesis may be achieved using the ABI 431A peptide synthesizer (Applied Biosystems). Additionally, the amino acid sequence of DME, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide or a polypeptide having a sequence of a naturally occurring polypeptide.

The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) Methods Enzymol. 182:392-421.) The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, supra, pp. 28-53.)

In order to express a biologically active DME, the nucleotide sequences encoding DME or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences encoding DME. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding DME. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding DME and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) Results Probl. Cell Differ. 20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding DME and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and

16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding DME. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. (See, e.g., Sambrook, supra; Ausubel, supra; Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509; Engelhard, E.K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945; Takamatsu, N. (1987) EMBO J. 6:307-311; The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196; Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659; and Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355.) Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. (See, e.g., Di Nicola, M. et al. (1998) Cancer Gen. Ther. 5(6):350-356; Yu, M. et al. (1993) Proc. Natl. Acad. Sci. USA 90(13):6340-6344; Buller, R.M. et al. (1985) Nature 317(6040):813-815; McGregor, D.P. et al. (1994) Mol. Immunol. 31(3):219-226; and Verma, I.M. and N. Somia (1997) Nature 389:239-242.) The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding DME. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding DME can be achieved using a multifunctional E. coli vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or PSPORT1 plasmid (Life Technologies). Ligation of sequences encoding DME into the vector's multiple cloning site disrupts the *lacZ* gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for in vitro transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509.) When large quantities of DME are needed, e.g. for the production of antibodies, vectors which direct high level expression of DME may be used. For example, vectors containing the strong, inducible SP6 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of DME. A number of vectors containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH promoters, may be used in the yeast Saccharomyces cerevisiae or Pichia pastoris. In addition, such

vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, supra; Bitter, G.A. et al. (1987) Methods Enzymol. 153:516-544; and Scorer, C.A. et al. (1994) Bio/Technology 12:181-184.)

Plant systems may also be used for expression of DME. Transcription of sequences encoding DME may be driven by viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al. (1984) Science 224:838-843; and Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105.) These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, e.g., The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, sequences encoding DME may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses DME in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of DME in cell lines is preferred. For example, sequences encoding DME can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in *tk*⁻ and *apr*⁻ cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers resistance to the aminoglycosides neomycin and G-418; and *als* and *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. USA 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. USA 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech), ß glucuronidase and its substrate ß-glucuronide, or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) Methods Mol. Biol. 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding DME is inserted within a marker gene sequence, transformed cells containing sequences encoding DME can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding DME under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

In general, host cells that contain the nucleic acid sequence encoding DME and that express DME may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

Immunological methods for detecting and measuring the expression of DME using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on DME is preferred, but a competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St. Paul

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Val Asp Glu Gly Leu Val Lys Ala Ile Gly Ile Ser Asn Phe Asn
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His Leu Gln Val Glu Arg Ile Leu Asn Lys Pro Asp Leu Lys Tyr
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<211> 1814
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte ID No: 7472775CB1

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Val Ile Pro Cys Gly Asp Leu Met Ala Glu Leu Leu Ala Val Pro
                155                 160                 165
Phe Val Leu Thr Leu Arg Ile Ser Val Gly Gly Asn Met Glu Arg
                170                 175                 180
Ser Cys Gly Lys Leu Pro Ala Pro Leu Ser Tyr Val Pro Val Pro
                185                 190                 195
Met Thr Gly Leu Thr Asp Arg Met Thr Phe Leu Glu Arg Val Lys
                200                 205                 210
Asn Ser Met Leu Ser Val Leu Phe His Phe Trp Ile Gln Asp Tyr
                215                 220                 225
Asp Tyr His Phe Trp Glu Glu Phe Tyr Ser Lys Ala Leu Gly Arg
                230                 235                 240
Pro Thr Thr Leu Cys Glu Thr Val Gly Lys Ala Glu Ile Trp Leu
                245                 250                 255
Ile Arg Thr Tyr Trp Asp Phe Glu Phe Pro Gln Pro Tyr Gln Pro
                260                 265                 270
Asn Phe Glu Phe Val Gly Gly Leu His Cys Lys Pro Ala Lys Ala
                275                 280                 285
Leu Pro Lys Glu Met Glu Asn Phe Val Gln Ser Ser Gly Glu Asp
                290                 295                 300
Gly Ile Val Val Phe Ser Leu Gly Ser Leu Phe Gln Asn Val Thr
                305                 310                 315
Glu Glu Lys Ala Asn Ile Ile Ala Ser Ala Leu Ala Gln Ile Pro
                320                 325                 330
Gln Lys Val Leu Trp Arg Tyr Lys Gly Lys Lys Pro Ser Thr Leu
                335                 340                 345
Gly Ala Asn Thr Arg Leu Tyr Asp Trp Ile Pro Gln Asn Asp Leu
                350                 355                 360
Leu Gly His Pro Lys Thr Lys Ala Phe Ile Thr His Gly Gly Met
                365                 370                 375
Asn Gly Ile Tyr Glu Ala Ile Tyr His Gly Val Pro Met Val Gly
                380                 385                 390
Val Pro Ile Phe Gly Asp Gln Leu Asp Asn Ile Ala His Met Lys
                395                 400                 405
Ala Lys Gly Ala Ala Val Glu Ile Asn Phe Lys Thr Met Thr Ser
                410                 415                 420
Glu Asp Leu Leu Arg Ala Leu Arg Thr Val Ile Thr Asp Ser Ser
                425                 430                 435
Tyr Lys Glu Asn Ala Met Arg Leu Ser Arg Ile His His Asp Gln
                440                 445                 450
Pro Val Lys Pro Leu Asp Arg Ala Val Phe Trp Ile Glu Phe Val
                455                 460                 465
Met Arg His Lys Gly Ala Lys His Leu Arg Ser Ala Ala His Asp
                470                 475                 480
Leu Thr Trp Phe Gln His Tyr Ser Ile Asp Val Ile Gly Phe Leu
                485                 490                 495
Leu Thr Cys Val Ala Thr Ala Ile Phe Leu Phe Thr Lys Cys Phe
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Leu Phe Ser Cys Gln Lys Phe Asn Lys Thr Arg Lys Ile Glu Lys
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Arg Glu
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<210> 2
<211> 523
<212> PRT
<213> Homo sapiens

<220>
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<223> Incyte ID No: 2516747CD1

<400> 2

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Gly Val Leu Leu Ser Glu Ala Ala Lys Ile Leu Thr Ile Ser Thr
            20                  25                  30
Leu Gly Gly Ser His Tyr Leu Leu Leu Asp Arg Val Ser Gln Ile
        35                  40                  45
Leu Gln Glu His Gly His Asn Val Thr Met Leu His Gln Ser Gly
    50                  55                  60
Lys Phe Leu Ile Pro Asp Ile Lys Glu Glu Glu Lys Ser Tyr Gln
65                  70                  75
Val Ile Arg Trp Phe Ser Pro Glu Asp His Gln Lys Arg Ile Lys
                80                  85                  90
Lys His Phe Asp Ser Tyr Ile Glu Thr Ala Leu Asp Gly Arg Lys
            95                  100                 105
Glu Ser Glu Ala Leu Val Lys Leu Met Glu Ile Phe Gly Thr Gln
        110                 115                 120
Cys Ser Tyr Leu Leu Ser Arg Lys Asp Ile Met Asp Ser Leu Lys
    125                 130                 135
Asn Glu Asn Tyr Asp Leu Val Phe Val Glu Ala Phe Asp Phe Cys
140                 145                 150
Ser Phe Leu Ile Ala Glu Lys Leu Val Lys Pro Phe Val Ala Ile
155                 160                 165
Leu Pro Thr Thr Phe Gly Ser Leu Asp Phe Gly Leu Pro Ser Pro
                170                 175                 180
Leu Ser Tyr Val Pro Val Phe Pro Ser Leu Leu Thr Asp His Met
            185                 190                 195
Asp Phe Trp Gly Arg Val Lys Asn Phe Leu Met Phe Phe Ser Phe
        200                 205                 210
Ser Arg Ser Gln Trp Asp Met Gln Ser Thr Phe Asp Asn Thr Ile
    215                 220                 225
Lys Glu His Phe Pro Glu Gly Ser Arg Pro Val Leu Ser His Leu
230                 235                 240
Leu Leu Lys Ala Glu Leu Trp Phe Val Asn Ser Asp Phe Ala Phe
245                 250                 255
Asp Phe Ala Arg Pro Leu Leu Pro Asn Thr Val Tyr Ile Gly Gly
            260                 265                 270
Leu Met Glu Lys Pro Ile Lys Pro Val Pro Gln Asp Leu Asp Asn
        275                 280                 285
Phe Ile Ala Asn Phe Gly Asp Ala Gly Phe Val Leu Val Ala Phe
    290                 295                 300
Gly Ser Met Leu Asn Thr His Gln Ser Gln Glu Val Leu Lys Lys
305                 310                 315
Met His Asn Ala Phe Ala His Leu Pro Gln Gly Val Ile Trp Thr
            320                 325                 330
Cys Gln Ser Ser His Trp Pro Arg Asp Val His Leu Ala Thr Asn
        335                 340                 345
Val Lys Ile Val Asp Trp Leu Pro Arg Ser Asp Leu Leu Ala His
    350                 355                 360
Pro Ser Ile Arg Leu Phe Val Thr His Gly Gly Gln Asn Ser Val
365                 370                 375
Met Glu Ala Ile Arg His Gly Val Pro Met Val Gly Leu Pro Val
            380                 385                 390
Asn Gly Asp Gln His Gly Asn Met Val Arg Val Val Ala Lys Asn
        395                 400                 405
Tyr Gly Val Ser Ile Arg Leu Asn Gln Val Thr Ala Asp Thr Leu
    410                 415                 420
Thr Leu Thr Met Lys Gln Val Ile Glu Asp Lys Arg Tyr Lys Ser
425                 430                 435
Ala Val Val Ala Ala Ser Val Ile Leu His Ser Gln Pro Leu Ser
            440                 445                 450
Pro Ala Gln Arg Leu Val Gly Trp Ile Asp His Ile Leu Gln Thr
        455                 460                 465
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Gly Gly Ala Thr His Leu Lys Pro Tyr Ala Phe Gln Gln Pro Trp
                470                 475                 480
His Glu Gln Tyr Leu Ile Asp Val Phe Val Phe Leu Leu Gly Leu
                485                 490                 495
Thr Leu Gly Thr Met Trp Leu Cys Gly Lys Leu Leu Gly Val Val
                500                 505                 510
Ala Arg Trp Leu Arg Gly Ala Arg Lys Val Lys Lys Thr
                515                 520
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<220>
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<400> 3

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Ser Glu Arg Ser Thr Arg Leu Leu Thr Lys Thr Ser His Ser Gln
                20                  25                  30
Gly Gly Asp Gln Ala Leu Ser Lys Ser Thr Gly Ser Pro Thr Glu
                35                  40                  45
Lys Leu Ile Glu Lys Arg Gln Gly Ala Lys Thr Val Phe Asn Lys
                50                  55                  60
Phe Ser Asn Met Asn Trp Pro Val Asp Ile His Pro Leu Asn Lys
                65                  70                  75
Ser Leu Val Lys Asp Asn Lys Trp Lys Lys Thr Glu Glu Thr Gln
                80                  85                  90
Glu Lys Arg Arg Ser Phe Leu Gln Glu Phe Cys Lys Lys Tyr Gly
                95                 100                 105
Gly Val Ser His His Gln Ser His Leu Phe His Thr Val Ser Arg
               110                 115                 120
Ile Tyr Val Glu Asp Lys His Lys Ile Leu Tyr Cys Glu Val Pro
               125                 130                 135
Lys Ala Gly Cys Ser Asn Trp Lys Arg Ile Leu Met Val Leu Asn
               140                 145                 150
Gly Leu Ala Ser Ser Ala Tyr Asn Ile Ser His Asn Ala Val His
               155                 160                 165
Tyr Gly Lys His Leu Lys Lys Leu Asp Ser Phe Asp Leu Lys Gly
               170                 175                 180
Ile Tyr Thr Arg Leu Asn Thr Tyr Thr Lys Ala Val Phe Val Arg
               185                 190                 195
Asp Pro Met Glu Arg Leu Val Ser Ala Phe Arg Asp Lys Phe Glu
               200                 205                 210
His Pro Asn Ser Tyr Tyr His Pro Val Phe Gly Lys Ala Ile Ile
               215                 220                 225
Lys Lys Tyr Arg Pro Asn Ala Cys Glu Glu Ala Leu Ile Asn Gly
               230                 235                 240
Ser Gly Val Lys Phe Lys Glu Phe Ile His Tyr Leu Leu Asp Ser
               245                 250                 255
His Arg Pro Val Gly Met Asp Ile His Trp Glu Lys Val Ser Lys
               260                 265                 270
Leu Cys Tyr Pro Cys Leu Ile Asn Tyr Asp Phe Val Gly Lys Phe
               275                 280                 285
Glu Thr Leu Glu Glu Asp Ala Asn Tyr Phe Leu Gln Met Ile Gly
               290                 295                 300
Ala Pro Lys Glu Leu Lys Phe Pro Asn Phe Lys Asp Arg His Ser
               305                 310                 315
Ser Asp Glu Arg Thr Asn Ala Gln Val Val Arg Gln Tyr Leu Lys
               320                 325                 330
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